REMARKS/ARGUMENTS.

Claim 32 has been withdrawn and claims 22-23 and 34-36 have been amended. Thus, claims 1-2, 4-10, 12, and 16-31, and 33-36 are currently pending. Clear support for the claim amendments are made in the specification on page 12, line 6 to page 33, line 20. Applicants respectfully submit that the amendments do not introduce new matter in contravention of 35 U.S.C. §132. Reconsideration is respectfully requested.

1. Claim 36.

Claim 36 stands rejected as being in improper dependent form. Claim 36 has been amended to follow the format of revised claims 34 and 35 (see 2 below). The objection in this regard is thus believed to have been overcome.

2. 35 USC §101: Claims 34-35.

Claims 34-35 stand rejected due to the "use" format. Claims 34-35 have been amended to read as method claims. The objection in this regard is thus believed to have been overcome.

3. 35 USC §112 First Paragraph Objections.

Claim 32 is objected-to in this regard. Claim 32 has been withdrawn, so this objection is believed no longer relevant.

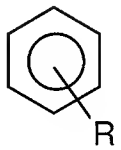
4. 35 USC §112 Second Paragraph Objections.

Claims 6-10, 12, 22-26, 32 and 34-35 stand rejected in this regard.

Claims 6 and 7.

The elliptical shape of Formula II shows that the imaging moiety can be attached at any point of the Formula [not just $(A)_n$]. The text of the specification describes that quite clearly at page 5 lines 6 to 20: the imaging moiety is either intrinsic to the chemical structure of the MMPi, or is attached as an additional species optionally *via* a linker group as for Formula II.

The ellipse of Formula II is a conventional chemical structure drawing for attachment at any position. An analogous presentation is benzene substituted at any position:



The Examiner's interpretation (specific attachment at A) is illogical because:

(i) the ellipse in Formula II would be redundant;

(ii) Formula II as written is consistent with chemical nomenclature and also the text of the specification, where the imaging moiety can be attached at a variety of positions.

The Examiner states that "X^a is defined as the imaging moiety". That is not the case. X^a of Formula II can be several substituents or X^9 is the imaging moiety [emphasis added]. It is thus clear from the text of the claim also that X^a is optionally the imaging moiety. When X^a

is not the imaging moiety, that means that the imaging moiety is attached elsewhere as shown in the ellipse of Formula II.

Applicants thus believe that claim 6 is suitable for allowance, and accordingly this objection should be withdrawn.

Claims 8-10, 12, 22 and 24-26.

The antecedent basis for "radioactive metal ion or paramagnetic metal ion in claim 8 is objected-to. Claim 8 has been revised to address this objection.

A similar clarifying amendment has been made to claim 22. The objection to claims 8 and 22, plus their dependent claims is thus believed to have been overcome.

Claim 23.

The dependency of previous claim 23 was erroneous. Reference to a "conjugate" clearly means that the correct claim should have been claim 22. Claim 23 has been amended accordingly.

The explanation for Formula II (claim 6 above) is also relevant here. The definition of X^a in Formula IIb has been corrected to clarify matters by changing to X^b.

Claim 32.

Claim 32 has been withdrawn, hence this objection is no longer relevant.

Claims 34-35.

These claims have been amended, and are believed to be no longer indefinite.

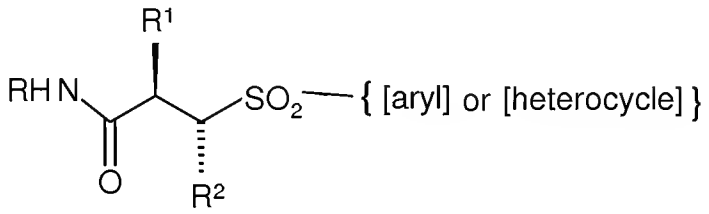
5. 35 USC §103 (Obviousness) Rejections.

All the current claims under consideration (1-2, 4-10, 12, 16-31, and 33-36) stand rejected as being obvious over the combination of either Carpenter *et al* (WO 01/60416) or Mobashery (WO 01/92244) in view of Sahagan (EP 1088550 A1).

The Examiner's position (page 15 of the present Office Action) is that a person skilled in the art would be motivated to prepare imaging agents based on compounds "structurally similar to those taught by Carpenter", and to use such imaging agents and/or kits for the diagnosis of cardiovascular diseases, especially atherosclerosis. [emphasis added]. The Examiner refers to the first structural formula of claim 31 – which also corresponds to the first such formula of claim 8 of Carpenter. In response, Applicants refer to the phrase "structurally similar to those taught by Carpenter". One must first recognize that such a teaching would be extremely broad, since Carpenter itself is already very broad in scope. Thus, claim 8 (and 31) of Carpenter recite two formulae, with definitions of options for the X, R and R^1 to R^{31} groups which run to several pages of text. That applies even for the claims, which should provide a summary of the scope of the invention. Carpenter describes the scope of the invention over pages 8 to 86 of his specification. Even when specific MMPis are described (page 86 line 30 to page 91 line 21), these are by class of inhibitor. These classes include "succinyl hydroxamate" (page 88 line 24); "sulfonamide hydroxamate" (page 89 lines 10-12) and "alanine hydroxamate" (page 89 lines 20-22). Carpenter also makes reference to multiple publications and patent applications, all of which are "incorporated by reference". Such incorporation broadens the scope yet further. The scope of "structurally similar to those taught by Carpenter" is thus vast. The Examiner has failed to justify what motivation

exists to select the specific group of compounds of the present claims, from the vast genus of compounds "structurally similar" to Carpenter, which would probably encompass millions of compounds. Applicants position is that, when such an enormous choice exists, the selection cannot be an obvious one.

Applicants furthermore point out that the closest formula of Carpenter appears to be:



where: the aryl or heterocycle groups can be substituted by 0-2 R^6 groups;

R^2 is C_{1-20} alkyl;

R^6 is aryloxy substituted with 0-3 R^7;

where R^7 is Hal or methoxy.

Even this formula has significant differences over Formula (I) of present claim 1, including:

(i) the SO_2 moiety is linked to 2 carbon atoms, constituting a sulfone. The compounds of the present claims are sulfonamides, since they comprise the $-NSO_2-$ moiety;

(ii) Carpenter has a single substituent at R^1. At the equivalent position, Formula II of present Claim 1 has 2 substituents (X^1 and X^2) which form a saturated ring system. Carpenter does not teach or suggest

more than one substituent at that position, let alone ring structures exclusively at that position;

(iii) the R group of Carpenter includes a thiol substituent (-CH_2SH), for which there is not counterpart in Formula II of present claim 1.

Applicants contend that items (i) – (iii) constitute more substantial changes than can be described as "structurally similar".

The Examiner suggests that Carpenter itself provides motivation for the person skilled in the art to prepare structurally similar imaging agents. Applicants question this logic. Carpenter provides 17 supporting Examples (pages 113 to 136). Carpenter discusses utility at pages 137-141. Whilst representative compounds are said to be active in *in vitro* assays (page 137, lines 28-30), there is no data which shows proof of concept for *in vivo* imaging. *In vivo* animal models of cardiovascular disease are discussed at page 140 line 9 following of Carpenter. That description is written in the present tense, i.e. is prophetic in nature. Carpenter leaves it to the person skilled in the art to test the efficacy of the vast range of imaging agents described therein. Carpenter provides no real data on any of the imaging agents claimed, so demonstration of efficacy for any of the *in vivo* imaging applications described is absent.

Applicants contend that the person skilled in the art of *in vivo* imaging would be well aware that behaviour in *in vitro* assays is no guarantee or predictor of behaviour in the mammalion body *in vivo*. In the absence of *in vivo* data, the person skilled in the art would not therefore be encouraged or motivated to consider building on the teaching of Carpenter.

Mobashery (WO 01/92244).

The Examiner argues (page 18 of the present invention) that Mobashery provides a person skilled in the art with motivation to develop MMPis conjugated to a detectable moiety for use in diagnosis of diseases associated with MMP activity.

Applicants respectfully disagree. Mobashery provides 6 supporting Examples (page 35 line 9 to page 43 line 30). All of the Examples are, however, just syntheses of the organic chemicals. Thus, Mobashery does not synthesize or test any radiolabelled compound. Example 7 of Mobashery provides *in vitro* enzyme inhibition data (Ki values) for Compounds 1-4, but those are unlabelled, non-radioactive compounds. Mobashery does not even provide a description of how the claimed radiolabelled compounds of the invention are to be prepared.

Given that the MMPis of Mobashery include relatively reactive functional groups, i.e. epoxides (also called oxiranes, where J = O), or thiiranes (J = S), there is a significant question mark over how a person skilled in the art could successfully radiolabel the compounds without unwanted side-reactions and consequent loss of biological activity.

Since no labeled compounds are described, and no data showing proof of concept for imaging are provided, applicants contend that the person skilled in the art could have no motivation to build other detectably labeled MMPis based on Mobashery.

Applicants stress that, in contrast to both Carpenter and Mobashery, the present invention does provide evidence of useful *in vivo* properties of labeled compounds of the invention. See Examples 22 to 27 (pages 60-64) of the present specification.

Combination with Sahagan.

The Examiner contends that the general motivation to use labeled MMPis for *in vivo* imaging comes from Carpenter/Mobashery. Together with the specific MMPi structures of Sahagan, that is alleged to lead to the subject matter of the present claims in an obvious manner.

Applicants first of all stress that, closer reading of Carpenter and Mobashery does not support any such motivation existing. The Examiner stated (page 20):

> "... Carpenter and Mobashery have already shown that these compounds can be successfully used for diagnostic purposes when conjugated to an imaging moiety".

As discussed for Carpenter and Mobashery individually (above), applicants fail to see that either document shows that a conjugated imaging moiety "can be successfully used for diagnostic purposes", The opposite is true, since neither document provides any real evidence of imaging utility, for a MMPi having a conjugated imaging moiety. The teachings of Carpenter and Mobashery refer to mere possibilities. In the case of Mobashery, it is far from clear even that any labeled compounds suitable for imaging were ever prepared. The purported motivation therefore cannot be found in Carpenter or Mobashery.

The question also arises as to whether the references are combinable. Sahagan read as a whole refers to medicaments for the treatment of a mammal, together with related prodrugs. Paragraph [0043] still refers to methods of treatment when referring to isotopically-labeled compounds, and states that the same atom would be used, but having a different atomic mass from that normally found in nature. Sahagan at [0043], page 10 lines 34-40, does refer to certain isotope labels such as ^{3}H and ^{14}C being useful for "substrate tissue distribution assays". Such radioisotopes would be intrinsic to the molecule, as taught by Sahagan to be an essential feature. ^{3}H and ^{14}C are not, however, suitable for medical imaging. The person skilled in the art would understand that from the definition of "imaging moiety" at page 5 lines 22-29 of the present specification, plus the fuller description from page 5 line 31 to page 8 line 16.

Carpenter teaches diagnostic agents which comprise a diagnostic metal; 1-10 MMPi targeting moieties, a chelator and an optional linking group. The concept underlying the imaging moieties of Carpenter is thus completely different to a change in atomic mass of a single atom. Such a change would contravene the clear teaching of Sahagan itself on the same atom. In such circumstances, applicants do not believe that the combination is valid, or that motivation to combine with Carpenter really exists.

Mobashery does teach a variety of detectable radionuclides, both metallic and non-metallic. As noted above, however, Sahagan teaches clearly the need for an intrinsic (to the chemical structure of the MMPi) radioisotope label which has uses in therapy. That would preclude most if not all of the radioisotopes taught by Mobashery. As noted above, however,

Mobashery is not really enabling for radioisotope labeling. Hence, the combination with Sahagan is believed to lack motivation for the person skilled in the art.

Accordingly, Applicants respectfully request that the Examiner withdrawal the rejections for claims 1-2, 4-10, 12, 16-31, and 33-36 under 35 U.S.C. §103(a) and direct that these claims be allowed.

6. Double Patenting.

Claims 1-2, 4-10, 12, 16-31, and 33-36 are provisionally rejected under the doctrine of obvious-type double patenting, as being unpatentable over claims 1-21, 24-28, 30-31 and 35 of copending US patent application 10/544945. In response, Applicants submit that a terminal disclaimer will be filed once the instant application is indicated to be allowable.

CONCLUSION

Upon entry of this Amendment, claims 1-2, 4-10, 12, 16-31, and 33-36 remain pending. Applicants submit that all outstanding issues have been addressed, and that claims 1-2, 4-10, 12, 16-31, and 33-36 are in condition for allowance, which action is earnestly solicited.

The Commissioner is hereby authorized to charge any fees under 37 CFR §1.16(j) or 37 CFR 1.136(a) which may be required, or credit any overpayment, to Deposit Account No. 502-665 in the name of GE Healthcare, Inc.

Should any other matters require attention prior to allowance of the application, it is requested that the Examiner contact the undersigned.

Respectfully submitted,

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